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RESEARCH ARTICLE

LUPUS ANTICOAGULANT AND SEVERE PRE-ECLAMPSIA OR ECLAMPSIA: A HOSPITAL-BASED CASE-CONTROL STUDY IN OUAGADOUGOU, BURKINA FASO

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ABSTRACT: Background: Antiphospholipid antibodies are recognized to be associated to thrombosis and obstetric complications. Preeclampsia is a frequent pregnancy complication in our context. The objective of our study was to determine the prevalence of lupus anticoagulant (LA) and its association with severe pre-eclampsia and eclampsia in Burkina Faso. **Methods:** We carried out a hospital-based unmatched case-control study including 86 women with severe preeclampsia or eclampsia and 87 controls. LA were diagnosed using Diluted Russel's Viper Venom time screening and confirmation tests. Positive lupus anticoagulant was defined if the screen to confirmation ratio was over 1.2. **Results**: The prevalence of LA was 22.1% in women with preeclampsia or eclampsia and 3.4% in control (OR = 6.12; 1.45 – 25.84; p = 0.014). The primigravida accounted for68.2% of positive LA and had 2.69 odds of being positive to lupus anticoagulant compared to multigravida (OR = 2.69; [1.04 – 6.97]; p = 0.042). The LA could be suspected to be a part of the aetiologies of obstetrical complications (cases of obstetric antiphospholipid syndrome) in four cases (4.6%) of study-group. **Conclusion**: We certainly failed to diagnosis all cases of obstetric antiphospholipid syndrome in our study population, since we screened only LA. It is necessary to implement complementary assays for antiphospholipid antibodies detection in order to improve the exploration of pregnancy complications and thrombotic diseases.

KEYWORD: Lupus anticoagulant – Preeclampsia – Antiphospholipid antibody -Diluted Russel's Viper Venom Time

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INTRODUCTION:

Antiphospholipid antibodies (aPLA) are a heterogeneous group of autoantibodies directed against anionic (cardiolipin, phosphatidylserine) or neutral (phosphatidylethanolamine) phospholipids as well as phospholipid-binding plasma.[1–3] More than 20 antibodies antiphospolipid-binding proteins have been described, but the most important and clinically relevant are lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-beta-2-glycoprotein I (anti-ß2-GPI) antibodies.[2,3]

The association between aPLA and a wide spectrum of symptoms including arterial and venous thrombosis was defined in the last four decades as the antiphospholipid or Hughes syndrome (APS).[4] Since then, many other clinical manifestations of almost all organs and tissues was seen to be associated with aPLA. Indeed, obstetric complications such as recurrent pregnancy losses, fetal deaths typically beyond the tenth week of gestation are now recognized to be associated to aPLA, even if in more often, the cause is undiagnosed. Such obstetrical complications associated with to aPLA are defined as obstetrical antiphospholid syndrome. The prevalence of aPLA in women with obstetrical complications is as high as 5 – 40 % versus 2 – 5% in non-complicated pregnancies.[5–7]The suggested mechanism is placental-thrombotic events that cause infarction of placental blood vessels.[8–10] Common pathological features include small placentas with decidual arteriopathy, infarctions in central portions of the placenta, abruption and intervillous thrombosis.[11–13]

Such conditions can occur during pre-eclampsia (PE) and eclampsia, the major causes of maternal and fetal morbidity and mortality that affect 2–7% of healthy nulliparous women.[12–14] PE is clinically divided into severe and mild PE. The syndrome is considered severe when hypertension and/or proteinuria are substantially elevated and/or when additional organs are involved, indicated by the presence of hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, fetal growth restriction or when maternal cerebral disturbances are present.[15]

In Burkina Faso, the in-hospital incidence of pre-eclampsia and eclampsia is about at least one case per day with a case fatality rate of 9.6%.[16] However, the relationship with aPLA was not investigated due to the unavailability of the biological diagnosis, as in many developing countries.[17] The objective of this study was to determine the prevalence of LA and its association to severe pre-eclampsia and eclampsia in Ouagadougou, Burkina Faso.

MATERIALS AND METHODS:

Study setting

We conducted between May and August 2019, a case-control study in two third level public referral hospitals (Yalgado Ouédraogo University Hospital Center – CHUYO and Tengandogo University Hospital Center - CHUT) and one second level referral hospital (the Protestant Schiphra Hospital). The maternity services of these three hospitals are among the eight largest in Ouagadougou. Study participants were recruited among pregnant women at least 20 weeks of gestation (WG) admitted in these maternity services for childbirth or pregnancy complications.

Case definition and study participants' recruitment

Severe pre-eclampsia was defined by a systolic blood pressure ≥ 160 mm Hg or a diastolic blood pressure ≥ 110 mm Hg measured on two occasions in a pregnant woman at more than 20 WG, associated with a sign of severity such as oliguria, proteinuria at 3+ dipstick, headache, visual disturbances, HELLP syndrome.[18–20] A woman with preeclampsia who has new-onset grand mal seizures is considered to have eclampsia.[18–20]

The obstetrical antiphospholipid syndrome was defined by a positive LA associated to at least one of the three following clinical criteria: i°) three or more consecutive spontaneous abortions before the 10th WG or ii°) one or more unexplained fetal deaths at or beyond the 10th WG or iii°) one or more preterm deliveries before the 34th WG due to eclampsia or severe preeclampsia.[21]

During a four months recruitment period in the three study sites, all pregnant women admitted for childbirth were examined by senior obstetrician gynecologists for suspicion and confirmation of the diagnosis of preeclampsia and eclampsia and information recorded on the patient's clinical file. Patients meeting the above cases' inclusion criteria and those meeting the controls' criteria (women in apparent good health without preeclampsia condition) were interviewed for inform consent and complementary data collection. Maternal characteristics and obstetric history were obtained using data collection sheets designed for this purpose. Useful details of the perinatal history and infant's standard anthropometric variables were collected from the maternity hospital records.

For both cases and controls, women with a history of high blood pressure, gestational hypertension, positive tests to human immunodeficiency and hepatitis B viruses, *Treponema pallidium*, anticoagulant therapy, coagulation factor deficiencies and any chronic inflammatory condition were not included.

Blood sampling

Blood samples were collected from both cases and controls between 24 hours and 42 days after delivery by clean venipuncture into aPLAstic tube containing 0.5 mL of 3.2% (0.109 M) trisodium citrate anticoagulant tube. The anticoagulant-to-blood ratio of 1 in 9 was considered. The tubes were mixed by gentle 3 to 5 successive inversion.

The samples were kept and transported at ambient temperature within 4 hours of collection time to the Charles De Gaulle pediatric University Hospital Center (CHUP-CDG) for laboratory tests. They were double centrifuged, first at 2270 g for 15 minutes at ambient temperature, followed by decantation in aPLAstic tube and a second centrifugation at 3000 g for 10 minutes. The platelet-poor plasma obtained were aliquoted, frozen and stored at - 30°C. Prior to use, plasma was thawed in a water bath for 5 minutes at 37 °C.

Lupus anticoagulant test algorithm and interpretation

The principle of LA detection is based on their ability to prolong the clotting time in phospholipid dependent coagulation assays as the dilute Russell's Viper Venom Time (dRVVT).[22–24] We performed analyzes using the SIEMENS® CA-600 hemostasis machine with SYSMEX®dRVVT reagents comprised of screening reagent LA1 (batch N° OQGP172) and confirmatory reagent LA2 (batch N° OQGR132). LA1 contains a clot activator and a reduced phospholipid content hence, creating competition for binding amongst clotting factors and circulating antiphospholipid antibodies. If antiphospholipid antibodies are present, the clotting time will be prolonged. LA2 contains the same activator with an excess of phospholipid. As there is sufficient phospholipid to support both antiphospholipid antibodies and clotting factor binding, the effect of the antiphospholipid antibodies is eliminated. Correction of the clotting time by the addition of excess phospholipid, confirms the presence of LA.[25] LA1 and LA2 were prepared using 2 mL and 1 mL of distilled water respectively and stored for maximum 48 hours at 2 to 8 °C.

The testing algorithm consisted firstly of the screening test. A dRVVT screen ratio is calculated by dividing the patient's dRVVT screen by the normal reference dRVVT. A dRVVT screen ratio >

1.20 indicated an abnormally prolonged clotting time and imposed dRVVT mix test (1:1 mixture of patient's plasma and normal plasma) and dRVVT confirmation test. The mix test was positive if it corrected the dRVVT (mix ratio ≤ 1.20) and would indicated the presence of inhibitors or deficiencies/dysfunctions of coagulation factors or any anticoagulant effect. In all cases, the presence of LA was confirmed if LA ratio (dRVVT screen ratio / dRVVTconfirmation ratio) > 1.20 or if the percentage correction of ratio (dRVVT screen ratio - dRVVTconfirmation ratio / dRVVT screen ratio) ≥ 10%.[26]

Statistical analyses

Data were entered into Epi-info software and exported into STATA 15 for analysis. Quantitative and qualitative variables were described using mean ± 2SD (Standard deviation) and proportion respectively. The chi-square test (or Fisher's exact test if indicated), student t test and Mann–Whitney U test were used to compare proportion, mean and median as appropriated. Associations of pre-eclampsia/eclampsia and positive LA (yes or no) with maternal and pregnancy characteristics were assessed using odd ratio (95% CI) in univariate and multivariate logistic regression. Differences were statistically significant for a $p < 0.05$.

Ethical considerations

Authorizations from the directorates-general and heads of maternity and laboratory services at the three hospitals were obtained before the start of the study. Informed consent was obtained from the patients. All data collected has been used anonymously and with respect for the rights and dignity of patients.

RESULTS:

Baseline characteristics of study groups

A total of 173 patients (86 cases and 87 controls) were included (Table 1). The mean age was almost the same in both groups with slightly more 20-years adolescents among the cases (p = 0.044).

There was as much history of miscarriages in both two groups (p = 0.973). The current pregnancy had lasted shorter (35.5 ± 4.1 versus 39.0 ± 1.0 weeks; p < 0.001) and more often resulted in abortion or premature delivery in cases than in controls (31.4% versus 0%; p <0.001). The 86 cases comprised of 61 women (70.9%) with severe preeclampsia and 23 cases of eclampsia. Two cases were complicated with HELLP syndrome.

Lupus anticoagulant and severe pre-eclampsia/eclampsia

Among the 28 patients (24 cases and 4 controls) with abnormally prolonged dRVVT screen, 19 cases and 3 controls (p < 0.001) were confirmed positive for LA (Table 1).

Table 1: Baseline characteristics of cases and controls included in the study

Parameter	Cases (n = 86)	Controls (87)	p-value
Age (year)			
Mean age (± 2SD)	25.3 ± 6.0	25.4 ± 4.9	0.548
Age group (n, %)			0.044
≤ 20	27 (31.4)	14 (16.1)	
21 – 25	19 (22.1)	32 (36.8)	
26 - 30	24 (27.9)	28 (32.2)	
31 – 35	10 (11.6)	11 (12.6)	
36 - 40	6 (7.0)	2 (2.3)	
Obstetric history			
Gravidity (n, %)			0.006
Primagravida	48 (55.8)	34 (39.1)	
Multigravida	25 (29.1)	46 (52.9)	
(2 – 4 pregnancies)	13 (15.1)	7 (8.0%)	
Grand multigravida (≥ 5 pregnancies)			

Miscarriage (n, %)	14 (16.3)	14 (16.1)	0.973
Multiple pregnancies (n, %)	9 (10.5)	1 (1.1)	0.009
Current pregnancy			
Mean gestational age (Weeks)	35.5 ± 4.1	39.0 ± 1.0	<0.001
Pregnancy outcome (n, %)			< 0.001
Miscarriages	10 (11.6)	0 (0.0)	
Preterm deliveries	17 (19.8)	0 (0.0)	
Term deliveries	59 (68.6)	87 (100)	
Laboratory tests			
Abnormal dRVVT screen (n, %)	24 (27.9)	4 (4.6)	< 0.001
Positive lupus anticoagulant (n, %)	19 (22.1)	3 (3.4)	< 0.001

Abbreviation: SD: Standard deviation; n: number; %: percentage; dRVVT: dilute Russell's Viper Venom Time

The median dRVVT screen (p < 0.001) and dRVVT confirmation (p = 0.490) in cases group were 48.85 sec [IQR: 41.5 – 53.4] and 41.95 sec [IQR: 41.55 – 45.85] versus 43.1 [IQR: 40.0 – 45.8] and 41.6 sec [IQR: 38.85 – 45.10] for controls (Figure 1).

Positive LA (OR = 6.12; 1.45 – 25.84, p = 0.014) was positively associated to pre-eclampsia and eclampsia (Table 2). The primagravida represented 68.2% of positive LA and had 2.69 odds of being LA positive compared to multigravida (OR = 2.69; [1.04 – 6.97]; p = 0.042). Among the group of cases, 28 patients (32.5%) had a preterm delivery before 34 WG, of which four (4.6% of 86 cases) were LA positive, thus meeting the diagnosis of obstetrical APS criteria. Recurrent miscarriages were not associated to LA (OR = 0.22; [0.03 – 1.70]).

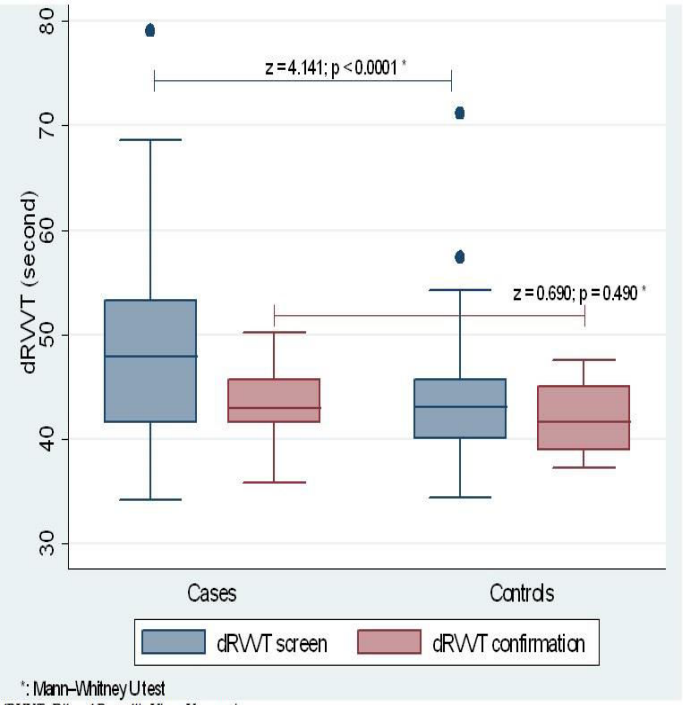

Figure 1. Comparison of screening and confirmation diluted Russell's viper venom times (medium with interquartile range) in women with severe preeclampsia / eclampsia and controls in Burkina Faso

Table 2: Risk factors at multivariate logistic regression associated to preeclampsia/eclampsia in women admitted for childbirth. (columns 2 to 6 concern univariate analysis and columns 7, 8 and 9 the multivariate analysis.)

Risk factors	Cases (n = 86)	Controls (n = 87)	Odd ratio	CI 95%	p-value	Odd ratio	CI 95%	p-value
Positive lupus anticoagulant	19	3	7.94	2.25 – 27.97	0.001	6.12	1.45 – 25.84	0.014
Recurrent miscarriages	14	14	1.01	0.45 – 2.28	0.973	1.72	0.50 – 5.95	0.388
Multiple pregnancies	9	1	10.05	1.24 – 81.17	0.030	9.20	0.87 – 97.70	0.065
Primigravidae	48	34	1.97	1.07 – 3.61	0.028	3.24	1.10 – 9.54	0.033
Gestational age	35.5 ± 4.1	39.0 ± 1.0	-	-	< 0.001	0.54	0.41 – 0.70	< 0.001
Age group								
≤ 20	27	14	Ref	-	-	Ref	-	-
21 – 25	19	32	0.31	0.13 – 0.73	0.007	0.67	0.22 – 2.04	0.480
26 - 30	24	28	0.44	0.19 – 1.03	0.060	1.26	0.35 – 4.47	0.719
31 – 35	10	11	0.47	0.16 – 1.38	0.169	0.90	0.19 – 4.26	0.896
36 - 40	6	2	1.55	0.28 – 8.73	0.616	1.98	0.17 – 23.42	0.589

DISCUSSION:

Our study aimed at assessing the prevalence of LA and its association with pre-eclampsia and eclampsia. To achieve this purpose, we performed an unmatched case-control study that included 86 cases and 87 controls. Positive LA was found in 22.1% of cases versus 3.4% among controls. There was positive association between LA and pre-eclampsia / eclampsia (OR = 6.12; 1.45 – 25.84, p = 0.014) and the current pregnancy ended earlier in cases group compared to controls (35.5 ± 4.1 versus 39.0 ± 1.0 WG, p < 0.001). The diagnosis of obstetrical APS was noted in 4.6% of cases.

To our knowledge, this study is the first that exploring this question. Thus, it provides important preliminary data on antiphospholipid antibodies, an "*etiology of certain obstetric complications that we do not often think about in Sub-Saharan Africa*", according to N'dhatz.[17] Through this study, the LA detection technique was implemented for the first time in a laboratory in Burkina Faso. This constitutes a new skills acquisition that will contribute to the management of hemostasis disorders in our country. However, our study had some limitations. Due to the lack of standardization of the tests and inter-laboratory variability, the International Society on Thrombosis and Haemostasis (ISTH) recommends that each laboratory uses its own reference values established from healthy volunteers.[23,27,28] Such cut-off were not yet established in our country. Moreover, women were not screened, neither for aCL nor for anti-αβ2GPI that are described to be more often associated to LA and now recognized as key-tools for better assessment of thrombosis risks and APS classification.[29,30]

The prevalence found in the two groups (22.1 % and 3.4%) were closed to those reported in Sub-Saharan Africa by some authors. Indeed, aPLA was estimated at 1 – 5% in general population.[21]In Nigeria, the frequency was 15.4% in women with preeclampsia and 2% in the control group.[31]However, another study in Benin city (Nigeria)[32]reported low frequencies, 10% versus 0% as those found in France (7.75% versus 2.58%).[33] The study population demographical and underlying clinical characteristics, the inter-laboratory variations (timing of sampling, methods used for aPLA analysis and performances of kits and cut off used) could have induced these differences. Another explanation could be the racial

or ethnic, geographical and genetic differences that were already exposed.[34,35]

The prevalence of LA was 6.5 times higher among at risky pregnant women compared to those who were not. Women with preeclampsia or eclampsia have 6.12 odds of being positive to LA (OR = 6.12; 1.45 – 25.84; p = 0.014). The association between preeclampsia and aPLA is well established by many authors. In France, women had 3.17 odds of having aPLAs (OR= 3.17 [1.07 - 9.34]) if they presented preeclampsia compared to those who were not.[33] But in this study, only IgG anti-αβ2GPI (but not LA) were associated with severe pre-eclampsia (OR= 16.91 [3.71 - 77.06]). Findings on association between LA and preeclampsia were too disparate according to study designs, LA screening methods. In Nigeria, two studies found no association with respectively infinite and 1.9 odds of detecting LA among preeclampsia women in case-control studies.[32,36] Another case-control study in France did not found any association between preeclampsia and aPLA, namely LA (OR = 0.86 [0.32 - 2.30] for all cases of preeclampsia and OR=1.02 [0.18 - 5.59] among severe preeclampsia).[37]However, a meta-analysis shown that LA (OR=2.34 [1.18 – 4.64]) as well as aCL (OR = 1.52 [1.05 – 2.2]) were associated to preeclampsia in case-control studies but not in cohort studies (OR = 5.17 [0.60 - 44.56] for LA and 1.78 [0.39 - 8.16] for aCL).[38] But They noted exactly the opposite for anti-αβ2GPI, i.e. an absence of association in the case-control studies (OR = 0.57 [0.32 – 1.04]) and a strong association in cohort studies (OR = 19.14 [6.34 - 57.77]).[38] A positive association was also found for LA (OR = 7 [1.5 – 33.8]) in USA.[39]

Among the above studies, some have applied the algorithm comprising at least two screening tests including an LA-sensitive test recommended by the ISHT[22,27,40–42], other have just used a single LA-sensitive test, mainly the dRVVT.[32] In all of these studies, the 1:1 mixture of patient's plasma and normal pooled plasma was performed for inhibition test and phospholipid-dependence confirmation test was made using a high phospholipid concentration dRVVT test[32,33] or platelet neutralization procedure.[37] Some of them performed ELISA tests for the diagnosis of anti-αβ2GPI or aCL.[32,33,37]

These disparities in the study's findings raise the problem of inter-laboratory variability in hemostasis analyzes and the absence of a relevant test validated for the diagnosis of LA. Indeed, three clotting time tests (LA sensible activated partial thromboplastin time - aPTT-LA sensible, dilute Russell's Viper Venom Time - dRVVT and diluted prothrombin time - dPT) are usually used for LA screening. Each of these test is influenced by coagulation genetic or acquired deficiencies or some medications. Also, false results could have occurred. The algorithm proposed by the ISHT recommends a three-stages analyze, 1°) an association of two LA-sensible tests at screening phase, 2°) a 1:1 mixture of patient's plasma and normal plasma for inhibition study and 3°) a confirmatory test with an enriched-phospholipid assay for phospholipid-dependence demonstration.[27,40–42] In our study, we used a single test (i.e. dRVVT screen) during the screening phase, associated with the mix and confirmatory tests; such an algorithm corresponded to the integrated test.[26,43]

The median dRVVT screen was significantly longer among cases than in controls (p < 0.0001) but not the LA ratio (p = 0.325). Among patients with abnormally prolonged dRVVT screen, approximately ¼ were tested negative for LA at confirmation stage. In Nigeria,[31]it was noted 38.5% of false positives using a confirmation strategy based on mix (80% normal plasma + 20% patient plasma) kaolin clotting time (KCT) as already described.[44]Ibrahim[36] found 62.5% false positives with 50:50 mix KCT. The intrinsic performances of LA tests for the diagnosis of obstetrical APS have already been questioned.[28–30] For example, Swadzba shown that aPTT and dRVVT had less strong association to pregnancy events (OR = 2.2

[1.1 – 4.3] and 2.3 [1.1 – 5.2] respectively) with a sensitivity of 30 and 21 % and a specificity of 84 and 90% respectively.[28] The different assays explore either the intrinsic or extrinsic pathway, or the common one. Also, the issues encountered are due to the genetic abnormalities or not, that affect each test.[43]

We could retain the diagnosis of obstetrical APS in 4.6% of preeclampsia/eclampsiagroup. Recurrent miscarriages (spontaneous abortions or fetal deaths) were not associated to preeclampsia (table 2) nor to positive LA. Other authorsfound an association between APS and preterm deliveries before 34 WG due to severe preeclampsia or eclampsia (OR 13.0; [1.5-110.3]).[39]Other onesreported association between aPLA with both recurrent abortions and preterm deliveries.[17,32,36,38]

CONCLUSION:

We found a relatively high frequency of positive LAs in women with preeclampsia and eclampsia.

However, despite the strong association of LA and severe preeclampsia, we noted that it can be suspected in the occurrence of obstetric complications (i.e. obstetrical APS) only in 4 cases. Failure to screen for other aPLA (mainly anti-αβ2GPI or aCL) has certainly limited the possibility of diagnosis of such cases, since the diagnostic criteria take them into account. Thus, even if the screening of aPLA using LA as a first step seems appropriate in our context, it will be necessary to quickly implement these other complementary assays. Also, the next studies could usefully focus on their validation, taking into account the need to define for each, our own laboratory cut-offs.

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